Hindawi Publishing Corporation
Asian Journal of Neuroscience
Volume 2014, Article ID 181325, 9 pages
http://dx.doi.org/10.1155/2014/181325

Review Article

Clinicotherapeutic Potential of Leptin in Alzheimer's Disease and Parkinson's Disease

Soumyabrata Munshi,[1] Vineet Kumar Khemka,[2] Kalpita Banerjee,[3] and Sasanka Chakrabarti[2]

[1] *Department of Neuroscience, Chicago Medical School, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064, USA*
[2] *Department of Biochemistry, Institute of Post-Graduate Medical Education & Research, 244B Acharya J. C. Bose Road, Kolkata 700020, India*
[3] *Department of Neuroscience, Burke-Cornell Medical Research Institute, 785 Mamaroneck Avenue, White Plains, NY 10605, USA*

Correspondence should be addressed to Sasanka Chakrabarti; profschakrabarti95@gmail.com

Received 29 May 2014; Accepted 21 July 2014; Published 13 August 2014

Academic Editor: Cristoforo Comi

Chronic neurodegenerative diseases are a group of devastating neurological disorders that result in significant morbidity and mortality in the elderly population worldwide. Recent researches have shown some interesting associations of the classical antiobesity hormone leptin with two most important neurodegenerative diseases—Alzheimer's disease (AD) and Parkinson's disease (PD). Although several clinical studies have found the procognitive and memory-enhancing role of this peptide hormone in leptin-deficient patients, surprisingly it has not been used in any clinical trials involving patients with developing or full-blown neurodegenerative conditions. This review article is an attempt to bring together the existing information about the clinical associations of leptin with AD and PD. It starts with the basic understanding of leptin action in the brain and its derangements in these diseases and eventually discusses the potential of this hormone as a neuroprotective agent in clinical scenario.

1. Introduction

Aging-related chronic neurodegenerative diseases constitute a spectrum of neurological disorders characterized by a gradual loss of neuronal functions resulting from the toxicity of accumulated misfolded proteins [1–5]. Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common diseases of this group inflicting mostly the elderly population worldwide. These devastating disorders of neuronal dysfunctions are characterized by cognitive decline, memory loss, autonomic disturbances, and motor impairment [6–12]. By far, although a lot of theories and therapeutic targets have been identified underlying these debilitating diseases and various risk factors have been implicated in their pathogenesis, this spectrum of challenging disorders remains an enigma to the physicians and the scientists. Aging has been accredited as the major risk factor for neurodegeneration and recently much attention has been focused simultaneously on the possible role of obesity in the pathogenesis of this group of disorders [13–15]. A possible entangled relationship among obesity, aging, and neurodegeneration has also been proposed in many studies [14, 15].

Leptin is a polypeptide hormone involved significantly in the well-established role of regulation of energy homeostasis and neuroendocrine functions of our body via its action on the hypothalamus [16, 17]. Recent studies have found an interesting role of this hormone in various neurological functions like regulation of hypothalamic neuronal excitability, inhibition of hippocampal neurons, regulation of activity of the mesolimbic dopaminergic system, and modulation of synaptic plasticity and novel antidepressant actions [17–20]. Many of these neurological properties of leptin are currently being probed in order to get a strong foothold of the therapeutic implications for neurological disorders.

The present paper discusses the various aspects of leptin as a potential therapeutic molecule in the treatment of neurodegeneration along with the findings of some recent clinical studies showing its association with this group of disorders followed by a review of the clinical trials using leptin and its prospect as therapeutic agent in neurodegenerative diseases.

2. Leptin Action in the Brain: Molecular Basis

Leptin is a 16 kDa polypeptide product of obese (*ob*) gene and is synthesized and secreted from the white adipose tissue of our body. On being released from the adipocytes, this peripherally derived leptin enters the central nervous system (CNS) via saturable transport across the blood brain barrier (BBB) and some leptin is synthesized locally in the specific regions of CNS like hypothalamus, cortex, and cerebellum as evidenced from the presence of leptin mRNA and protein in various parts of the brain [16, 18, 21]. Of the many leptin receptor (Ob-R) isoforms, Ob-Rb is the predominant signaling form and is present in many sites within CNS including hippocampus and cortex (affected mainly in AD) and in substantia nigra (affected mainly in PD) [22]. Ob-Rs are expressed both in the hypothalamic and in the extrahypothalamic sites [18, 23, 24]. The Ob-R lacks tyrosine kinase activity and acts via association with the Janus tyrosine kinase (JAK) by JAK/STAT and Ras-Raf-MAPK pathways [18]. The different signaling pathways that leptin acts through have been extensively elaborated elsewhere in a review article [23].

3. Impairment of Leptin Action with Aging

Studies involving aged rats have shown decrease in leptin response compared to their younger counterparts [22, 25]. This has been accounted for a number of reasons like reduction in the STAT3 activation downstream of the leptin receptor (Ob-R) signaling pathway, decrease in the Ob-R expression due to reduced uptake of leptin by the hypothalamic nuclei, impaired suppression of hypothalamic neuropeptide Y (NPY) mRNA levels, and increased inhibition of Ob-R signal transduction owing to the age-dependent increase in the level of suppressor of cytokine signaling-3 (SOCS-3) and protein tyrosine phosphatase 1B [25–29].

4. Aberrant Leptin Signaling in Neurodegenerative Diseases

Accumulation of amyloid beta (Aβ) and tau hyperphosphorylation within the CNS are implicated significantly in the pathogenesis of neurodegenerative diseases like AD and PD [30–32], and leptin affects these two vital processes [33]. Dysregulation of leptin signaling pathway and neuronal leptin resistance have been recently shown to underlie the pathophysiology of AD [33]. Ob-Rb trafficking to the cell membrane depends on proper functioning of microtubules, and tau protein is a microtubule associated protein [34, 35]. Findings by Bonda et al. suggest that, due to formation of neurofibrillary tangles (NFTs) by hyperphosphorylated tau proteins, the Ob-Rb leptin receptors cannot translocate to the neuronal cell membranes but get sequestered in the NFTs, thereby causing physical inaccessibility of leptin to its receptors [33]. The resultant decline of leptin signaling causes hypersecretion of leptin and hence its level in circulation increases under such circumstances [36].

5. Neuroprotective Functions of Leptin in Experimental Models

Many studies have demonstrated protection of neuronal cell loss and preservation of neuronal function by leptin [37–39]. Leptin prevents neuronal death by reducing Aβ levels both *in vitro* and *in vivo*, as well as by reducing tau hyperphosphorylation [40, 41]. The neuroprotective role of leptin has been extensively studied in both *in vitro* and *in vivo* models of neurodegeneration [42–44]. *In vitro* model of PD using cultured dopaminergic cells exposed to the neuronal toxin 6-hydroxydopamine (6-OHDA) has shown protection from death by leptin [39, 42]. *In vivo* study with animals treated with the same toxin has been shown to have greater number of surviving neurons in the substantia nigra when treated with leptin compared to controls [39]. In that study, it has been shown that leptin-induced CREB activation by MEK/ERK pathways causes increase in BDNF production that imparts the neuroprotective role of leptin [39]. That BDNF plays an important role in long-term potentiation (LTP), a form of synaptic plasticity, responsible for long-term memory (LTM) formation and synaptogenesis has been extensively reviewed elsewhere [45]. Hence leptin by increasing BDNF production has potential role in synaptogenesis and neuronal plasticity. Leptin has also been described to mediate its actions by JAK/STAT pathway [39]. Phosphoinositide 3 (PI3) kinase pathway, with the downstream targets of Akt and NF-κB, and MAP kinase pathways have been shown to be the targets of leptin-mediated neuroprotective effects in neurodegenerative studies [42]. In a study using cultured hippocampal neurons, it has been shown that leptin reduced superoxide production and stabilized mitochondrial transmembrane potential [40], and since reactive oxygen species and mitochondrial dysfunction play significant roles in the pathogenesis of neurodegenerative diseases [46], leptin has an important role in prevention of the neuronal death in this group of diseases. The various mechanisms of such protective effects of leptin that have been proposed in that study include activation of mitochondrial manganese superoxide dismutase and expression of antiapoptotic protein Bcl-xL leading to stabilization of mitochondrial transmembrane potential and promotion of transcription of uncoupling protein 2 (UCP2), all of which act towards reduction of superoxide production [40]. Leptin has also been identified as an inhibitor of β-secretase (β-site APP cleaving enzyme, BACE) and hence it reduces the formation of Aβ formation [21, 47]; a very recent study by Marwarha et al. has shown that in a sirtuin SIRT1-dependent manner, leptin mediates this effect by reducing the acetylation of Lys 310 residue in the p65 subunit of NF-κB, thereby reducing the NF-κB mediated transcription and expression of BACE1 [48]. The disruption of the lipid raft structure, thereby hindering the interaction

of amyloid precursor protein (APP) with BACE, has also been proposed as the underlying mechanism for inhibition of BACE activity by leptin [47]. Recent studies have shown that direct injection of leptin into the hippocampus of rodents improves memory processing and modulates LTP and synaptic plasticity via selective enhancement of N-methyl-D-aspartate (NMDA) responses by activation of PI3K, MAPK, and/or Src tyrosine kinase [49]. Improved memory following leptin administration has also been found in SAMP-8 mice, an accelerated senescence rodent model that develops amyloid plaques [37]. Chronic leptin administration to the APP-overexpressing mouse, Tg2576, by implanted miniosmotic pumps reduced brain amyloid levels significantly [44, 47]. In a recent study by Doherty et al., it has been shown that leptin reverses the Aβ inhibition of hippocampal LTP, reduces Aβ-induced facilitation of long-term depression (LTD) by PI3 kinase pathway, protects against Aβ-induced internalization of glutamate receptor 1 subunit (GluR1) by PI3 kinase-dependent mechanism thereby preventing removal of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors from the synapses in hippocampal neurons, protects cortical neuronal death against Aβ-mediated toxicity by STAT3-mediated pathway, and reduces Aβ-induced expression of synaptic protein endophilin 1 and phosphorylated tau in cortical neurons both *in vitro* and *in vivo* [50]. These interesting findings suggest potential beneficial effects of leptin in both early and late stages of AD [50]. The different effects of leptin on the morphology and functions of the neurons are shown schematically in Figure 1.

6. Leptin and Neuroinflammatory Basis of AD and PD

Many studies uphold the neuroinflammatory hypothesis of AD and PD [51, 52]. Studies have shown microglial activation in the substantia nigra [53] and locus coeruleus [54] of postmortem PD brains [55]. Several studies have shown the presence of CD8+ and CD4+ T lymphocytes in the brain regions affected in PD [53, 56]. Cytokine production and oxidative stress have been implicated in the pathogenesis of PD as well [46, 52]. Similarly, neuroinflammatory basis of AD has been evidenced in many studies as reviewed elsewhere [52]. In a brain ischemia model in rat, it has been shown that leptin causes neuroprotective effects by early regulation of reactive astrocytes via increasing STAT3 phosphorylation [57]. Leptin has been associated with inflammation and immune response in humans and animals. In the periphery, leptin is known to affect many aspects of immune response and inflammation like induction of chemotaxis of neutrophils, increase in the CD4+/CD8+ lymphocytes, T helper 1 cells differentiation, and development of natural killer (NK) cells [58]. One study has proposed that, in response to inflammation, the acute phase reactant C-reactive protein that is produced by hepatocytes in the periphery binds to circulating leptin and reduces the effects of leptin in the brain, thereby creating a leptin-resistant state in the body [58]. Leptin in pharmacological concentrations also induces the production of proinflammatory cytokines like IL-1β, IL-6, and TNF-α and contributes to different responses to inflammation [58, 59]. IL-1 is a major proinflammatory cytokine and activation of its signaling pathways plays an important role in the defense responses against inflammation in the body including the brain [59]. It has been shown that primary rat microglial cells express leptin receptors [59]. Leptin targets microglial cells in the brain causing synthesis and release of IL-1β and its naturally occurring receptor antagonist IL-1RA [59]. IL-1RA is present in the brain and circulation of normal humans and rodents [59]. Thus whether the effect of leptin on the brain will be proinflammatory or anti-inflammatory will depend on the relative concentrations of IL-1 and IL-1RA produced by the action of leptin. Astrocytes, the most abundant glial cell type in the brain, get activated in response to various inflammatory stimuli and cause upregulation of proinflammatory cytokines [60]. They play an important role in the neuroinflammatory basis of neurodegenerative diseases like AD [60]. Leptin receptor and mRNA have been shown in rat brain astrocytes along with the changes in the expression of leptin receptors in cultured C6 astrocytoma cells in response to proinflammatory stimuli [61]. Thus it is possible that leptin acts on these inflammatory cells in the brain and modulates neuroinflammatory processes in an intricate manner. The neuroprotective effects of leptin as seen in various studies may, therefore, have a potential anti-inflammatory basis, and it will be interesting to explore this aspect of leptin in experimental models of AD and PD.

7. Effects of Leptin on Dopamine Actions: The PD Connection

The degeneration of both the mesostriatal and mesolimbic dopaminergic pathways has been suggested to be involved in PD [62]. Various studies have mainly focused on leptin effects on the mesolimbic dopamine function and feeding behavior [63–65]. A strong association between plasma leptin and cerebrospinal fluid (CSF) dopamine levels ($r = 0.74$; $P < 0.01$) in humans has been shown in one study [66]. Leptin receptors are present in dopaminergic neurons in midbrain [67, 68] and leptin acts directly on these neurons [63]. Leptin has been shown to modulate D2 receptor expression in striatum, and a unique interaction between the leptin receptors and D2 receptors exists in these neurons in mice [64]. Although these results indicate a potential role of leptin in regulating the action of dopamine in the brain, the exact molecular mechanisms of such actions of leptin are yet to be elucidated.

8. Effects of Leptin on Myelination: The AD Connection

Although not included within the defining histopathological features of AD, the degeneration of white matter is a usual finding in postmortem AD brain [69, 70]. There is a growing body of evidence to indicate that the disruption of myelin and injury to oligodendrocytes could play a major role in the neurodegeneration of AD and interestingly the process primarily affects the late-myelinating neurons which show

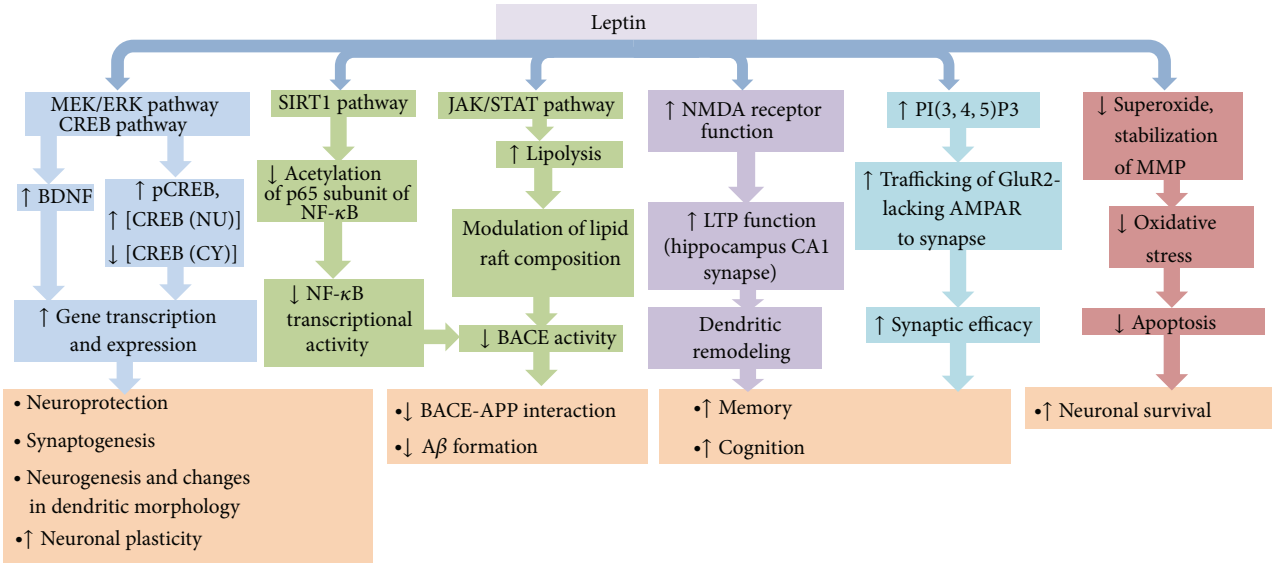

Figure 1: Effects of leptin on neuronal health and functions. The schematic diagram shows different pathways by which leptin exerts its neuroprotective, procognitive, memory-enhancing, and other beneficial effects on neuronal health and morphology. NU: nuclear; CY: cytosolic; MMP: mitochondrial membrane potential.

a very protracted phase of myelination beginning from early brain development to well into midlife [71]. The white matter damage in the late-myelinating tracts in AD brain is also supported by *in vivo* imaging techniques using diffusion tensor imaging (DTI) or white matter tract integrity (WMTI) metrics, and further the Pittsburgh compound B (PIB) imaging of Aβ peptides confirms the antemortem deposition of Aβ peptides in the late-myelinating regions of the brain [72, 73]. In the brain of transgenic AD mice, such lesions in myelin and oligodendroglia have been noticed even before the onset of significant Aβ or tau pathology [74]. Very conspicuous age-related disruption of myelin in the sensorimotor areas of brain and optic nerve has been observed by electron microscopy, though there is clear evidence of continued remyelination in the aged CNS [75, 76]. Further, the microarray hybridization analysis and quantitative polymerase chain reaction (qPCR) studies have revealed significant alterations in the expressions of genes related to lipid metabolism, neurotransmitter transport, and immune response in the optic nerve of aged rats [75]. Since aging is the most dominant risk factor for AD, such age-related changes may be causally linked to disruption of brain myelin observed in postmortem AD brain. The multiple implications of myelin disruption and repair with AD pathogenesis such as Aβ accumulation, oligomerization and toxicity, altered APP and BACE1 expression, accumulation and hyperphosphorylation of tau, and axonal and synaptic dysfunctions have been well presented in a recent review, but the evidence apparently is not compelling enough for claiming myelin dysfunction as a major driving force for the genesis and progress of AD [77]. However, several aspects need vigorous exploration in this context. For example, it has been pointed out that oligodendrocytes and myelin are enriched in iron and the disruption of myelin may release reactive metal which can promote oxidative damage and Aβ oligomerization and toxicity [73, 77]. Likewise, the vulnerability of oligodendrocytes to hypoperfusion, oxygen radicals, products of activated microglia, and other toxic insults or the alterations in cholesterol turnover and trafficking within the brain as a result of myelin injury and repair could be important determinants in AD pathology [77]. Similarly, Aβ42-induced caspase activation and apoptosis in mouse oligodendrocyte precursor cell line are crucial evidence linking myelin disruption with AD pathology [78]. The role of leptin in regulating myelin synthesis during brain development has been indicated in several studies over the years. Leptin deficiency in genetically obese (*ob*/*ob*) mice leads to reduced brain weight and impaired myelination with altered fatty acid composition, and further in such mutant mice the expression of myelin basic protein, proteolipid protein, and glial fibrillary acidic protein is diminished in neocortex, hippocampus, and striatum [79, 80]. Such changes in myelin proteins have also been observed in leptin-resistant state in diabetic dyslipidemic (*db*/*db*) mice [80]. The effect of leptin administration in reversing impaired myelination or altered expression of myelin proteins in *ob*/*ob* mice is somewhat inconsistent. It is reported that injection of leptin daily from 4 to 10 weeks of age in *ob*/*ob* mice does not reverse the decreased expression of myelin proteins in these mice, although the weight and protein content of the brain and expression levels of several neuronal proteins show significant improvement [80]. However, in a recent study, leptin administration in young *ob*/*ob* mice has been shown to increase the expression of myelin basic protein and the density of myelinated axons without increasing the thickness of myelin sheath [81]. Thus, further detailed explorations are needed to understand the regulatory role of leptin on myelination of brain in early postnatal life and more importantly on myelin repair or recycling in adult or aged brain.

9. Clinical Studies: Leptin, Cognition, and Memory

Studies have shown a strong inverse association of AD and dementia with leptin levels. In a large population-based prospective cohort study involving 785 persons without dementia, higher leptin levels have been found to be associated with reduced risk of AD over a median follow-up period of 8.3 years [82]. The same study has also shown in a subset of the cohort that the elevated plasma leptin is associated with higher cerebral volume as evaluated with magnetic resonance imaging [82]. Another large-scale prospective study of 2871 elderly (age: 70–79 years) participants has demonstrated that higher circulating leptin level is protective against cognitive decline [83]. A recent study comprised of 60 cases and 60 controls showed lower levels of circulating leptin in AD subjects as well as its strong positive correlation with the severity of the dementia [84]. Similarly, several other case-control studies have confirmed that lower serum leptin is associated with AD [85–87]. Contradicting this, a small study has shown no change in serum leptin levels in AD patients compared to controls [88]. Similarly, another cross-sectional study involving 150 AD patients and 197 normal controls has failed to find any significant difference in the leptin levels between these two groups [89]. With regard to case-control studies it is important to remember that donepezil, an acetylcholinesterase inhibitor (AChEI) currently used in AD therapy, tends to lower the serum leptin levels [90, 91]. A recent study has also shown that renin-angiotensin system blockers might play a beneficial role in AD subjects by modulating the serum leptin level and slowing down cognitive decline [92].

Isolated studies have shown lower serum leptin levels in PD patients [93, 94]. Fiszer et al. in their study involving 11 PD patients with unintentional weight loss, 16 patients with no weight loss, and 12 control subjects have shown that the mean leptin concentration in plasma is lower in PD patients with weight loss as well as in all PD patients than in control subjects [93]. Likewise, another study has reported a lower, but statistically nonsignificant, serum leptin level in weight-losing PD subjects than their weight-stable counterparts [95]. A case-control study in Turkish PD subjects has shown that serum leptin levels do not correlate with disease progression or clinical severity but correlate with the age of the PD patients with younger patients having lower mean leptin levels [96]. Another recent study has shown no change in serum leptin level in PD patients compared to controls and also failed to establish any correlation between serum leptin and clinical or demographic data [97].

10. Leptin Replacement and Clinical Trials

Several clinical studies with leptin replacement therapy have been undertaken sporadically by certain groups in order to improve the neuronal functions in leptin-deficient patients. One such study showed improvement in the gray matter tissue concentration in the anterior cingulate gyrus, inferior parietal lobule, and cerebellum in three genetically leptin-deficient adults 6 months after initiation of recombinant methionyl human leptin (r-metHuLeptin) administration subcutaneously, and it was found to be sustained for over 18 months [98]. These results persisted for more than 3 years of leptin replacement and were reversed after a few weeks of withdrawal of leptin [38]. The cognitive enhancing role of leptin has also been seen in a young leptin-deficient boy who was put on a single daily evening dose of r-metHuLeptin treatment (to mimic the physiological circadian rhythm with nocturnal rise as seen with endogenous leptin) from the age of 5 years and 1 month and evaluated twice in two years [99]. Procognitive effects of leptin were noted in the child after such leptin treatment as was evident from improvements in various subsets of the Differential Ability Scale (DAS) and neuropsychological assessment (NEPSY) [38, 99]. These trials and findings point to the role of leptin in improving the neurocognitive functions of human brain.

Very recently, in February 2014, synthetic analog of leptin (known as metreleptin) has received approval from the United States Food and Drug Administration (FDA) for the treatment of generalized lipodystrophy [100]. However, the two dreaded and potential side effects of its treatment are risk of lymphoma and development of anti-leptin antibodies [100]. In spite of its immense beneficial roles in improvement of neuronal functions as evident from the cell-based and animal-based preclinical studies as well as from clinical trials in leptin-deficient conditions, leptin has not yet found place in clinical trials with neurodegenerative patients.

11. Future Prospective

The approved drugs for AD comprising three anticholinesterases (donepezil, galantamine, and rivastigmine) and one antiexcitotoxic (regulating glutamate activity) agent (memantine) appear to be extremely inadequate in halting this devastating neurodegenerative disorder. Moreover, recent clinical trials targeting Aβ peptide have failed to produce any significant clinical benefit [101]. The treatment opportunity for PD is somewhat better, but the patient eventually becomes nonresponsive to the treatment with L-3,4-dihydroxyphenylalanine (L-DOPA) or anticholinergic agents, and so forth, and the drug side effects become increasingly troublesome [9, 102]. For both AD and PD, the identification of new disease-modifying drugs is, therefore, imperative. The emerging role of leptin in the pathogenesis of AD and PD supported by both experimental and epidemiological studies allows us to envisage a novel therapeutic approach for the treatment of these neurodegenerative disorders. However, large-scale placebo-controlled and well-designed clinical trials with special attention to the timing of treatment initiation, duration of treatment, suitable monitoring by biomarker assay, imaging studies or clinical evaluation, and finally identification of long-term toxicity of administered leptin will be necessary.

Abbreviations

AD: Alzheimer's disease
APP: Amyloid precursor protein
Aβ: Amyloid beta
BACE: β-Site APP cleaving enzyme
BDNF: Brain-derived neurotrophic factor
CREB: cAMP response-element binding protein
ERK: Extracellular signal-regulated kinase
JAK: Janus kinase
LTP: Long-term potentiation
MAPK: Mitogen-activated protein kinase
MEK: MAPK/ERK kinase
NF-κB: Nuclear factor-kappa B
NFT: Neurofibrillary tangle
PD: Parkinson's disease
PI3: Phosphoinositide 3
SOCS: Suppressor of cytokine signaling
STAT: Signal transducer and activator of transcription.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

Soumyabrata Munshi is supported by a full scholarship and a complete tuition waiver in the Ph.D. Program at the Rosalind Franklin University of Medicine and Science. Vineet Kumar Khemka thanks The West Bengal University of Health Sciences for help and assistance. Kalpita Banerjee is supported by a Postdoctoral Fellowship at the Burke-Cornell Medical Research Institute, Weill Cornell Medical College. Sasanka Chakrabarti acknowledges the Department of Science and Technology, Government of India, and the Indian Council of Medical Research, New Delhi, India, for their support to research involving brain aging and neurodegeneration.

References

[1] J. P. Taylor, J. Hardy, and K. H. Fischbeck, "Toxic proteins in neurodegenerative disease," *Science*, vol. 296, no. 5575, pp. 1991–1995, 2002.

[2] C. Soto and L. D. Estrada, "Protein misfolding and neurodegeneration," *Archives of Neurology*, vol. 65, no. 2, pp. 184–189, 2008.

[3] P. Brundin, R. Melki, and R. Kopito, "Prion-like transmission of protein aggregates in neurodegenerative diseases," *Nature Reviews Molecular Cell Biology*, vol. 11, no. 4, pp. 301–307, 2010.

[4] M. Takalo, A. Salminen, H. Soininen, M. Hiltunen, and A. Haapasalo, "Protein aggregation and degradation mechanisms in neurodegenerative diseases," *American Journal of Neurodegenerative Disease*, vol. 2, pp. 1–14, 2013.

[5] J. L. Guo and V. M. Lee, "Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases," *Nature Medicine*, vol. 20, pp. 130–138, 2014.

[6] S. T. O'Keeffe, H. Kazeem, R. M. Philpott, J. R. Playfer, M. Gosney, and M. Lye, "Gait disturbance in Alzheimer's disease: a clinical study," *Age and Ageing*, vol. 25, no. 4, pp. 313–316, 1996.

[7] D. Aarsland, K. Andersen, J. P. Larsen et al., "The rate of cognitive decline in Parkinson disease," *Archives of Neurology*, vol. 61, no. 12, pp. 1906–1911, 2004.

[8] S. Della Sala, H. Spinnler, and A. Venneri, "Walking difficulties in patients with Alzheimer's disease might originate from gait apraxia," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 75, no. 2, pp. 196–201, 2004.

[9] M. Samuel, I. Maidment, M. Boustani, and C. Fox, "Clinical management of Parkinson's disease dementia: pitfalls and progress," *Advances in Psychiatric Treatment*, vol. 12, no. 2, pp. 121–129, 2006.

[10] C. H. Williams-Gray, T. Foltynie, S. J. G. Lewis, and R. A. Barker, "Cognitive deficits and psychosis in Parkinson's disease: a review of pathophysiology and therapeutic options," *CNS Drugs*, vol. 20, no. 6, pp. 477–505, 2006.

[11] J. Jankovic, "Parkinson's disease: Clinical features and diagnosis," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 79, no. 4, pp. 368–376, 2008.

[12] O. Wirths and T. A. Bayer, "Motor impairment in Alzheimer's disease and transgenic Alzheimer's disease mouse models," *Genes, Brain and Behavior*, vol. 7, supplement 1, pp. 1–5, 2008.

[13] H. Chen, S. M. Zhang, M. A. Schwarzschild, M. A. Hernán, W. C. Willett, and A. Ascherio, "Obesity and the risk of Parkinson's disease," *The American Journal of Epidemiology*, vol. 159, no. 6, pp. 547–555, 2004.

[14] M. Kivipelto, T. Ngandu, L. Fratiglioni et al., "Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease," *Archives of Neurology*, vol. 62, no. 10, pp. 1556–1560, 2005.

[15] K. Sriram, S. A. Benkovic, D. B. Miller, and J. P. O'Callaghan, "Obesity exacerbates chemically induced neurodegeneration," *Neuroscience*, vol. 115, no. 4, pp. 1335–1346, 2002.

[16] I. A. Arnoldussen, A. J. Kiliaan, and D. R. Gustafson, "Obesity and dementia: adipokines interact with the brain," *European Neuropsychopharmacology*, 2014.

[17] J. Harvey, "Leptin regulation of neuronal morphology and hippocampal synaptic function," *Frontiers in Synaptic Neuroscience*, vol. 5, article 3, 2013.

[18] J. Harvey, "Leptin regulation of neuronal excitability and cognitive function," *Current Opinion in Pharmacology*, vol. 7, no. 6, pp. 643–647, 2007.

[19] L. J. Shanley, D. O'Malley, A. J. Irving, M. L. Ashford, and J. Harvey, "Leptin inhibits epileptiform-like activity in rat hippocampal neurones via PI 3-kinase-driven activation of BK channels," *Journal of Physiology*, vol. 545, no. 3, pp. 933–944, 2002.

[20] X. Y. Lu, C. S. Kim, A. Frazer, and W. Zhang, "Leptin: a potential novel antidepressant," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, pp. 1593–1598, 2006.

[21] D. Beccano-Kelly and J. Harvey, "Leptin: A novel therapeutic target in Alzheimer's disease?" *International Journal of Alzheimer's Disease*, vol. 2012, Article ID 594137, 7 pages, 2012.

[22] G. H. Doherty, "Obesity and the ageing brain: could leptin play a role in neurodegeneration?" *Current Gerontology and Geriatrics Research*, vol. 2011, Article ID 708154, 8 pages, 2011.

[23] G. Marwarha and O. Ghribi, "Leptin signaling and Alzheimer's disease," *American Journal of Neurodegenerative Disease*, vol. 1, pp. 245–265, 2012.

[24] B. Burguera, M. E. Couce, J. Long et al., "The long form of the leptin receptor (OB-Rh) is widely expressed in the human brain," *Neuroendocrinology*, vol. 71, no. 3, pp. 187–195, 2000.

[25] P. J. Scarpace, M. Matheny, R. L. Moore, and N. Tümer, "Impaired leptin responsiveness in aged rats," *Diabetes*, vol. 49, no. 3, pp. 431–435, 2000.

[26] C. Fernández-Galaz, T. Fernández-Agulló, F. Campoy et al., "Decreased leptin uptake in hypothalamic nuclei with ageing in Wistar rats," *Journal of Endocrinology*, vol. 171, no. 1, pp. 23–32, 2001.

[27] Z. Wang, Y. Zhou, T. Kakuma et al., "Leptin resistance of adipocytes in obesity: role of suppressors of cytokine signaling," *Biochemical and Biophysical Research Communications*, vol. 277, no. 1, pp. 20–26, 2000.

[28] S. Peralta, J. M. Carrascosa, N. Gallardo, M. Ros, and C. Arribas, "Ageing increases SOCS-3 expression in rat hypothalamus: effects of food restriction," *Biochemical and Biophysical Research Communications*, vol. 296, no. 2, pp. 425–428, 2002.

[29] C. D. Morrison, C. L. White, Z. Wang et al., "Increased hypothalamic protein tyrosine phosphatase 1B contributes to leptin resistance with age," *Endocrinology*, vol. 148, no. 1, pp. 433–440, 2007.

[30] P. Lei, S. Ayton, D. I. Finkelstein, P. A. Adlard, C. L. Masters, and A. I. Bush, "Tau protein: relevance to Parkinson's disease," *International Journal of Biochemistry and Cell Biology*, vol. 42, no. 11, pp. 1775–1778, 2010.

[31] D. J. Irwin, V. M. Lee, and J. Q. Trojanowski, "Parkinson's disease dementia: convergence of α-synuclein, tau and amyloid-β pathologies," *Nature Reviews Neuroscience*, vol. 14, no. 9, pp. 626–636, 2013.

[32] G. Marwarha, B. Dasari, J. P. R. Prabhakara, J. Schommer, and O. Ghribi, "β-Amyloid regulates leptin expression and tau phosphorylation through the mTORC1 signaling pathway," *Journal of Neurochemistry*, vol. 115, no. 2, pp. 373–384, 2010.

[33] D. J. Bonda, J. G. Stone, S. L. Torres et al., "Dysregulation of leptin signaling in Alzheimer disease: evidence for neuronal leptin resistance," *Journal of Neurochemistry*, 2013.

[34] M. Wilcke and E. Walum, "Characterization of leptin intracellular trafficking," *European Journal of Histochemistry*, vol. 44, no. 4, pp. 325–334, 2000.

[35] R. J. Castellani, A. Nunomura, H. Lee, G. Perry, and M. A. Smith, "Phosphorylated tau: toxic, protective, or none of the above," *Journal of Alzheimer's Disease*, vol. 14, no. 4, pp. 377–383, 2008.

[36] S. P. Kalra, "Central leptin insufficiency syndrome: An interactive etiology for obesity, metabolic and neural diseases and for designing new therapeutic interventions," *Peptides*, vol. 29, no. 1, pp. 127–138, 2008.

[37] S. A. Farr, W. A. Banks, and J. E. Morley, "Effects of leptin on memory processing," *Peptides*, vol. 27, no. 6, pp. 1420–1425, 2006.

[38] G. Paz-Filho, M.-L. Wong, and J. Licinio, "The procognitive effects of leptin in the brain and their clinical implications," *International Journal of Clinical Practice*, vol. 64, no. 13, pp. 1808–1812, 2010.

[39] Z. Weng, A. P. Signore, Y. Gao et al., "Leptin protects against 6-hydroxydopamine-induced dopaminergic cell death via mitogen-activated protein kinase signaling," *Journal of Biological Chemistry*, vol. 282, no. 47, pp. 34479–34491, 2007.

[40] I. Martins, S. Gomes, R. O. Costa et al., "Leptin and ghrelin prevent hippocampal dysfunction induced by Aβ oligomers," *Neuroscience*, vol. 241, pp. 41–51, 2013.

[41] S. J. Greco, S. Sarkar, J. M. Johnston et al., "Leptin reduces Alzheimer's disease-related tau phosphorylation in neuronal cells," *Biochemical and Biophysical Research Communications*, vol. 376, no. 3, pp. 536–541, 2008.

[42] G. H. Doherty, C. Oldreive, and J. Harvey, "Neuroprotective actions of leptin on central and peripheral neurons *in vitro*," *Neuroscience*, vol. 154, no. 4, pp. 1297–1307, 2008.

[43] S. J. Greco, K. J. Bryan, S. Sarkar et al., "Leptin reduces pathology and improves memory in a transgenic mouse model of Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 19, no. 4, pp. 1155–1167, 2010.

[44] N. Tezapsidis, J. M. Johnston, M. A. Smith et al., "Leptin: A novel therapeutic strategy for Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 16, no. 4, pp. 731–740, 2009.

[45] C. Cunha, R. Brambilla, and K. L. Thomas, "A simple role for BDNF in learning and memory?" *Frontiers in Molecular Neuroscience*, vol. 3, article 1, 2010.

[46] S. Jana, M. Sinha, D. Chanda et al., "Mitochondrial dysfunction mediated by quinone oxidation products of dopamine: Implications in dopamine cytotoxicity and pathogenesis of Parkinson's disease," *Biochimica et Biophysica Acta*, vol. 1812, no. 6, pp. 663–673, 2011.

[47] D. C. Fewlass, K. Noboa, F. X. Pi-Sunyer, J. M. Johnston, S. D. Yan, and N. Tezapsidis, "Obesity-related leptin regulates Alzheimer's Aβ," *The FASEB Journal*, vol. 18, no. 15, pp. 1870–1878, 2004.

[48] G. Marwarha, S. Raza, C. Meiers, and O. Ghribi, "Leptin attenuates BACE1 expression and amyloid-β genesis via the activation of SIRT1 signaling pathway," *Biochimica et Biophysica Acta*, vol. 1842, no. 9, pp. 1587–1595, 2014.

[49] J. Harvey, L. J. Shanley, D. O'Malley, and A. J. Irving, "Leptin: a potential cognitive enhancer?" *Biochemical Society Transactions*, vol. 33, no. 5, pp. 1029–1032, 2005.

[50] G. H. Doherty, D. Beccano-Kelly, S. D. Yan, F. J. Gunn-Moore, and J. Harvey, "Leptin prevents hippocampal synaptic disruption and neuronal cell death induced by amyloid β," *Neurobiology of Aging*, vol. 34, no. 1, pp. 226–237, 2013.

[51] H. Wilms, L. Zecca, P. Rosenstiel, J. Sievers, G. Deuschl, and R. Lucius, "Inflammation in Parkinson's diseases and other neurodegenerative diseases: cause and therapeutic implications," *Current Pharmaceutical Design*, vol. 13, no. 18, pp. 1925–1928, 2007.

[52] G. Cappellano, M. Carecchio, T. Fleetwood, L. Magistrelli, R. Cantello, and U. Dianzani, "Immunity and inflammation in neurodegenerative diseases," *The American Journal of Neurodegener Diseases*, vol. 2, pp. 89–107, 2013.

[53] P. L. McGeer, S. Itagaki, B. E. Boyes, and E. G. McGeer, "Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains," *Neurology*, vol. 38, no. 8, pp. 1285–1291, 1988.

[54] E. Bertrand, W. Lechowcz, G. M. Szpak, and J. Dymecki, "Qualitative and quantitative analysis of locus coeruleus neurons in Parkinson's disease," *Folia Neuropathologica*, vol. 35, no. 2, pp. 80–86, 1997.

[55] E. C. Hirsch and S. Hunot, "Neuroinflammation in Parkinson's disease: a target for neuroprotection?" *The Lancet Neurology*, vol. 8, no. 4, pp. 382–397, 2009.

[56] V. Brochard, B. Combadière, A. Prigent et al., "Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease," *The Journal of Clinical Investigation*, vol. 119, no. 1, pp. 182–192, 2009.

[57] D. Amantea, C. Tassorelli, R. Russo et al., "Neuroprotection by leptin in a rat model of permanent cerebral ischemia: effects on STAT3 phosphorylation in discrete cells of the brain," *Cell Death and Disease*, vol. 2, no. 12, article e238, 2011.

[58] J. Li, F. Li, and A. Zhao, "Inflammation and leptin," *Drug Discovery Today: Disease Mechanisms*, vol. 3, no. 3, pp. 387–393, 2006.

[59] E. Pinteaux, W. Inoue, L. Schmidt, F. Molina-Holgado, N. J. Rothwell, and G. N. Luheshi, "Leptin induces interleukin-1β release from rat microglial cells through a caspase 1 independent mechanism," *Journal of Neurochemistry*, vol. 102, no. 3, pp. 826–833, 2007.

[60] C. Li, R. Zhao, K. Gao et al., "Astrocytes: implications for neuroinflammatory pathogenesis of Alzheimer's disease," *Current Alzheimer Research*, vol. 8, no. 1, pp. 67–80, 2011.

[61] H. Hsuchou, W. Pan, M. J. Barnes, and A. J. Kastin, "Leptin receptor mRNA in rat brain astrocytes," *Peptides*, vol. 30, no. 12, pp. 2275–2280, 2009.

[62] G. Chinaglia, F. J. Alvarez, A. Probst, and J. M. Palacios, "Mesostriatal and mesolimbic dopamine uptake binding sites are reduced in Parkinson's disease and progressive supranuclear palsy: a quantitative autoradiographic study using [3H]mazindol," *Neuroscience*, vol. 49, no. 2, pp. 317–327, 1992.

[63] D. M. Opland, G. M. Leinninger, and M. G. Myers Jr., "Modulation of the mesolimbic dopamine system by leptin," *Brain Research*, vol. 1350, pp. 65–70, 2010.

[64] J. Pfaffly, M. Michaelides, G. Wang, J. E. Pessin, N. D. Volkow, and P. K. Thanos, "Leptin increases striatal dopamine D2 receptor binding in leptin-deficient obese (*ob/ob*) mice," *Synapse*, vol. 64, no. 7, pp. 503–510, 2010.

[65] R. D. Palmiter, "Is dopamine a physiologically relevant mediator of feeding behavior?" *Trends in Neurosciences*, vol. 30, no. 8, pp. 375–381, 2007.

[66] M. M. Hagan, P. J. Havel, R. J. Seeley et al., "Cerebrospinal fluid and plasma leptin measurements: covariability with dopamine and cortisol in fasting humans," *The Journal of Clinical Endocrinology and Metabolism*, vol. 84, no. 10, pp. 3579–3585, 1999.

[67] D. P. Figlewicz, S. B. Evans, J. Murphy, M. Hoen, and D. G. Baskin, "Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat," *Brain Research*, vol. 964, no. 1, pp. 107–115, 2003.

[68] J. D. Hommel, R. Trinko, R. M. Sears et al., "Leptin receptor signaling in midbrain dopamine neurons regulates feeding," *Neuron*, vol. 51, no. 6, pp. 801–810, 2006.

[69] M. Sjöbeck, M. Haglund, and E. Englund, "Decreasing myelin density reflected increasing white matter pathology in Alzheimer's disease—a neuropathological study," *International Journal of Geriatric Psychiatry*, vol. 20, no. 10, pp. 919–926, 2005.

[70] B. T. Hyman, C. H. Phelps, T. G. Beach et al., "National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease," *Alzheimer's and Dementia*, vol. 8, no. 1, pp. 1–13, 2012.

[71] G. Bartzokis, "Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease," *Neurobiology of Aging*, vol. 25, no. 1, pp. 5–18, 2004.

[72] A. Benitez, E. Fieremans, J. H. Jensen et al., "White matter tract integrity metrics reflect the vulnerability of late- myelinating tracts in Alzheimer's disease," *NeuroImage: Clinical*, vol. 4, pp. 64–71, 2013.

[73] G. Bartzokis, P. H. Lu, and J. Mintz, "Human brain myelination and amyloid beta deposition in Alzheimer's disease," *Alzheimer's and Dementia*, vol. 3, no. 2, pp. 122–125, 2007.

[74] M. K. Desai, K. L. Sudol, M. C. Janelsins, M. A. Mastrangelo, M. E. Frazer, and W. J. Bowers, "Triple-transgenic Alzheimer's disease mice exhibit region-specific abnormalities in brain myelination patterns prior to appearance of amyloid and tau pathology," *GLIA*, vol. 57, no. 1, pp. 54–65, 2009.

[75] F. Xie, H. Fu, J. C. Zhang, X. F. Chen, X. L. Wang, and J. Chen, "Gene profiling in the dynamic regulation of the lifespan of the myelin sheath structure in the optic nerve of rats," *Molecular Medicine Reports*, vol. 10, pp. 217–222, 2014.

[76] F. Xie, P. Liang, H. Fu, J. C. Zhang, and J. Chen, "Effects of normal aging on myelin sheath ultrastructures in the somatic sensorimotor system of rats," *Molecular Medicine Reports*, vol. 10, no. 1, pp. 459–466, 2014.

[77] G. Bartzokis, "Alzheimer's disease as homeostatic responses to age-related myelin breakdown," *Neurobiology of Aging*, vol. 32, no. 8, pp. 1341–1371, 2011.

[78] M. K. Desai, M. A. Mastrangelo, D. A. Ryan, K. L. Sudol, W. C. Narrow, and W. J. Bowers, "Early oligodendrocyte/myelin pathology in Alzheimer's disease mice constitutes a novel therapeutic target," *The American Journal of Pathology*, vol. 177, no. 3, pp. 1422–1435, 2010.

[79] A. Sena, L. L. Sarlieve, and G. Rebel, "Brain myelin of genetically obese mice," *Journal of the Neurological Sciences*, vol. 68, no. 2-3, pp. 233–244, 1985.

[80] R. S. Ahima, C. Bjorbæk, S. Osei, and J. S. Flier, "Regulation of neuronal and glial proteins by leptin: implications for brain development," *Endocrinology*, vol. 140, no. 6, pp. 2755–2762, 1999.

[81] R. Hashimoto, A. Matsumoto, J. Udagawa, K. Hioki, and H. Otani, "Effect of leptin administration on myelination in *ob/ob* mouse cerebrum after birth," *NeuroReport*, vol. 24, no. 1, pp. 22–29, 2013.

[82] W. Lieb, A. S. Beiser, R. S. Vasan et al., "Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging," *The Journal of the American Medical Association*, vol. 302, no. 23, pp. 2565–2572, 2009.

[83] K. F. Holden, K. Lindquist, F. A. Tylavsky, C. Rosano, T. B. Harris, and K. Yaffe, "Serum leptin level and cognition in the elderly: findings from the Health ABC Study," *Neurobiology of Aging*, vol. 30, no. 9, pp. 1483–1489, 2009.

[84] V. K. Khemka, D. Bagchi, K. Bandyopadhyay et al., "Altered serum levels of adipokines and insulin in probable Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 41, no. 2, pp. 525–533, 2014.

[85] D. A. Power, J. Noel, R. Collins, and D. O'Neill, "Circulating leptin levels and weight loss in Alzheimer's disease patients," *Dementia and Geriatric Cognitive Disorders*, vol. 12, no. 2, pp. 167–170, 2001.

[86] A. A. Rizoulis, S. E. Karaoulanis, K. A. Rizouli, and A. Papadimitriou, "Serum leptin levels in patients with Alzheimers disease," *Internation Journal of Caring Sciences*, vol. 5, pp. 43–49, 2012.

[87] B. Bigalke, B. Schreitmüller, K. Sopova et al., "Adipocytokines and CD34+ progenitor cells in Alzheimer's disease," *PLoS ONE*, vol. 6, no. 5, Article ID e20286, 2011.

[88] A. Theodoropoulou, I. C. Metallinos, A. Psyrogiannis, G. A. Vagenakis, and V. Kyriazopoulou, "Ghrelin and leptin secretion in patients with moderate Alzheimer's disease," *Journal of Nutrition, Health and Aging*, pp. 1–6, 2012.

[89] M. W. Warren, L. S. Hynan, M. F. Weiner et al., "Lipids and adipokines as risk factors for Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 29, no. 1, pp. 151–157, 2012.

[90] K. János, P. Magdolna, J. Anna et al., "Achetylcholinesterase (AchE) inhibition and serum lipokines in Alzheimer's disease: friend or foe?" *Neuropsychopharmacologia Hungarica*, vol. 14, no. 1, pp. 19–27, 2012.

[91] M. Pakaski, A. Feher, and A. Juhasz, "Serum adipokine levels modified by donepezil treatment in Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 38, pp. 371–377, 2014.

[92] Y. Furiya, M. Ryo, M. Kawahara, T. Kiriyama, M. Morikawa, and S. Ueno, "Renin-angiotensin system blockers affect cognitive decline and serum adipocytokines in Alzheimer's disease," *Alzheimer's & Dementia*, vol. 9, pp. 512–518, 2013.

[93] U. Fiszer, M. Michałowska, B. Baranowska et al., "Leptin and ghrelin concentrations and weight loss in Parkinson's disease," *Acta Neurologica Scandinavica*, vol. 121, no. 4, pp. 230–236, 2010.

[94] B. Lorefält, G. Toss, and A. Granérus, "Weight loss, body fat mass, and Leptin in Parkinson's disease," *Movement Disorders*, vol. 24, no. 6, pp. 885–890, 2009.

[95] V. G. H. Evidente, J. N. Caviness, C. H. Adler, K. A. Gwinn-Hardy, and R. E. Pratley, "Serum leptin concentrations and satiety in Parkinson's disease patients with and without weight loss," *Movement Disorders*, vol. 16, no. 5, pp. 924–927, 2001.

[96] B. Ozdilek and G. Kenangil, "Serum leptin concentrations in Turkish Parkinson's disease population," *Parkinson's Disease*, vol. 2014, Article ID 576020, 5 pages, 2014.

[97] N. P. Rocha, P. L. Scalzo, I. G. Barbosa et al., "Circulating levels of adipokines in Parkinson's disease," *Journal of the Neurological Sciences*, vol. 339, pp. 64–68, 2014.

[98] J. A. Matochik, E. D. London, B. O. Yildiz et al., "Effect of leptin replacement on brain structure in genetically leptin-deficient adults," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 5, pp. 2851–2854, 2005.

[99] G. J. Paz-Filho, T. Babikian, R. Asarnow et al., "Leptin replacement improves cognitive development," *PLoS ONE*, vol. 3, no. 8, Article ID e3098, 2008.

[100] G. Sinha, "Leptin therapy gains FDA approval," *Nature Biotechnology*, vol. 32, pp. 300–302, 2014.

[101] J. H. Toyn and M. K. Ahlijanian, "Interpreting Alzheimer's disease clinical trials in light of the effects on amyloid-β," *Alzheimer's Research & Therapy*, vol. 6, article 14, 2014.

[102] B. Thanvi, N. Lo, and T. Robinson, "Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment," *Postgraduate Medical Journal*, vol. 83, no. 980, pp. 384–388, 2007.